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Swiss Public Assessment Report

Camzyos

International non-proprietary name: mavacamten
Pharmaceutical form: hard capsules
Dosage strength(s): 2.5 mg, 5 mg, 10 mg, 15 mg
Route(s) of administration: oral
Marketing authorisation holder: Bristol-Myers Squibb SA
Marketing authorisation no.: 68477
Decision and decision date: approved on 25.04.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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Table of contents

1 Terms, Definitions, Abbreviations 3
2 Background Information on the Procedure 5
2.1 Applicant's Request(s) 5
2.2 Indication and dosage 5
2.2.1 Requested indication 5
2.2.2 Approved indication 5
2.2.3 Requested dosage 5
2.2.4 Approved dosage 5
2.3 Regulatory history (milestones) 5
3 Medical context 6
4 Quality aspects 7
4.1 Drug substance 7
4.2 Drug product 7
4.3 Quality conclusions 8
5 Non-clinical aspects 9
5.1 Pharmacology 9
5.2 Pharmacokinetics 10
5.3 Toxicology 10
5.4 Non-clinical conclusions 11
6 Clinical and clinical pharmacology aspects 12
6.1 Clinical pharmacology 12
6.2 Dose finding and dose recommendation 17
6.3 Efficacy 17
6.4 Safety 18
6.5 Final clinical and clinical pharmacology benefit risk assessment 18
7 Risk management plan summary 20
8 Appendix 21

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BID	Twice daily (Latin: bis in die)
CL/F	Apparent clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EDP	End-diastolic pressure
EDV	End-diastolic volume
eGFR	Estimated glomerular filtration rate
EM	Extensive metabolisers
EMA	European Medicines Agency
ERA	Environmental risk assessment
F	Bioavailability
FDA	Food and Drug Administration (USA)
FS	Fractional shortening
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMR	Geometric mean ratio
HCM	Hypertrophic cardiomyopathy
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
Ka	Absorption rate constant
Ki	Inhibitory constant
LoQ	List of Questions
LVEF	Left ventricular ejection fraction
LVFS	Left ventricular fractional shortening
LVOT	Left ventricular outflow tract
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
nHCM	Non-obstructive HCM
NM	Normal metabolisers
NO(A)EL	No observed (adverse) effect level
NYHA	New York Heart Association
oHCM	Obstructive HCM
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
P-gp	P-glycoprotein

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PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PM	Poor metabolisers
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	Once daily (Latin: quaque die)
RM	Rapid metabolisers
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UM	Ultra rapid metabolisers

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for mavacamten in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 3 August 2021.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

2.2.2 Approved indication

Camzyos is indicated for the treatment of adult patients with symptomatic (NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) to improve functional capacity and associated symptoms (see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
An oral 5 mg once-daily starting dose of mavacamten that may be titrated up or down in a step-wise manner to result in a stable daily dose of 2.5, 5, 10, or 15 mg is recommended. Dose titration takes place with physician supervision based on echocardiogram monitoring of Valsalva left ventricular outflow tract (LVOT) gradient and left ventricular ejection fraction (LVEF) for efficacy and safety, respectively.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	18 October 2021
Formal control completed	4 November 2021
List of Questions (LoQ)	10 March 2022
Response to LoQ	7 June 2022
Preliminary decision	16 September 2022
Response to preliminary decision	14 November 2022
Labelling corrections	7 February 2023
Response to labelling corrections	28 February 2023
Final decision	25 April 2023
Decision	approval

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3 Medical context

Cardiomyopathies are a heterogeneous group of heart disorders characterised by structural and functional abnormalities of the myocardium. Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium (60-70%) caused by gene mutations of the cardiomyocytes. The 2 subclasses of HCM are obstructive HCM (oHCM) and non-obstructive HCM (nHCM). Both subclasses of HCM are characterised based on the presence or absence of left ventricular outflow tract (LVOT) obstruction, defined as peak LV outflow gradient ≥ 30 mmHg at rest or using provocation. These structural and functional abnormalities can produce a variety of symptoms, including dyspnoea fatigue, chest pain, palpitations, presyncope, or syncope.

The proportion of subjects with HCM who have oHCM ranges from 22% to 70%. In all age categories, men had a numerically higher prevalence than women. Assuming an approximate 70% proportion of subjects with HCM have the obstructive phenotype, prevalence of symptomatic oHCM in the adult population is below 5 in 10,000.

Limited pharmacological and surgical options to treat the chronic and progressive symptoms of oHCM leave an unmet medical need for a targeted therapy that addresses the underlying disease pathophysiology of oHCM. None of the current standard treatments of oHCM tackles the disease-specific or sarcomere-targeted therapies for oHCM.

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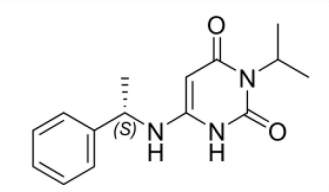
4 Quality aspects

4.1 Drug substance

INN: Mavacamten
Chemical name: 6-[[(1S)-1-phenylethyl]amino]-3-propan-2-yl-1H-pyrimidine-2,4-dione
Molecular formula: $C_{15}H_{19}N_3O_2$
Molecular mass: 273.33 g/mol
Molecular structure:



Physico-chemical properties:
Mavacamten is a white to off-white solid. It contains a chiral centre. Mavacamten is slightly soluble in water and is non-hygroscopic. The compound exhibits polymorphism. The commercial manufacturing process yields the anhydrous form A.

Synthesis:
The synthesis of mavacamten consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials, critical steps, and intermediates.

Specification:
The drug substance specification includes tests for appearance, identification, enantiomeric impurity, assay, organic impurities, total impurities, residue on ignition, water content, particle size distribution, polymorphic form, residual solvents, and microbial enumeration. The applied limits are justified and in line with the relevant guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:
The stability of the drug substance was investigated with commercial scale batches which were manufactured by the proposed commercial manufacturing site. The stability samples were stored under long-term conditions (25°C/60% rh) and accelerated conditions (40°C/75% rh) as defined in the corresponding ICH Guideline on stability studies. Based on these studies, an adequate retest period was defined.

4.2 Drug product

Description and composition:
Camzyos is an oral immediate release capsule, supplied in four dosage strengths, 2.5 mg, 5 mg, 10 mg, and 15 mg, in size 2 hard gelatin capsules, differentiated by the colour of the capsule caps (light purple/yellow/pink/grey) and the imprint of dosage strengths on the capsule caps.

Pharmaceutical development:
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.

Manufacture:

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The standard manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data and including batch manufacturing formula and in-process controls.

Specification:
The drug product specification covers relevant physico-chemical characteristics, as well as identification, assay, and purity tests. They allow for proper control of the drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the finished product.

Container closure system:
The hard gelatin capsules are packaged in blisters.

Stability:
Appropriate stability data have been generated for the drug product in the packaging material intended for marketing and following the relevant international guidelines. The data show good stability of the finished drug product and allow for a distinct assignment of the shelf life.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Non-clinical aspects

The non-clinical development programme for Camzyos with the new active substance mavacamten followed relevant ICH guidelines. The pivotal studies for safety assessment were performed in compliance with GLP regulations.

5.1 Pharmacology

In vitro, mavacamten was tested against myosin derived from slow-twitch, fast-twitch, smooth, and cardiac muscle, and against human cardiac myosin with various known pathogenic hypertrophic cardiomyopathy (HCM) mutations. Mavacamten decreased the steady-state enzymatic (ATP turnover) activity of human cardiac myosin in the basal, acto-myosin, and reconstituted Ca^{2+}-regulated soluble thin-filament systems, as well as in cardiac myofibrils (IC_{50} 0.52 to 0.73 µM). Comparable IC_{50} values were found for various pathogenic HCM mutations (0.65 to 1.31 µM). Mavacamten showed specificity for cardiac muscle when compared to skeletal isoforms and did not inhibit the smooth-muscle myosin isoform. Mavacamten inhibited the myosin-nucleotide complex regardless of the actin concentration present. Mavacamten inhibited the actin-activated ATPase activity (IC_{50} 0.47 µM) and phosphate (Pi) release (IC_{50} 0.46 µM) in purified bovine cardiac myosin subfragment-1 (myosin-S1) and bovine cardiac actin. These inhibitory effects were reversible, as dilution restored ATPase activity. The observation of a correlation of slowing steady-state ATPase rate with the Pi release rate suggested that the primary mechanism of action of mavacamten is the inhibition of the phosphate release step in the chemo-mechanical cycle. Mavacamten decreased the overall enzymatic activity of myosin heads in the disordered-relaxed (DRX) state in a dose-dependent manner, suggesting a reduction in the number of myosin heads readily available to form cross-bridges. Consequently, it increased the population of myosin heads in an energy-sparing super-relaxed (SRX) state (EC_{50} 1.2 to 1.9 µM). Mavacamten inhibited the actin gliding velocities with an IC_{50} of 0.24 µM, preventing the reduction of actin filament lengths with increasing concentrations. These results are in agreement with the above-mentioned mechanism of action of mavacamten, which results in fewer cardiac active cross-bridges and therefore reduces the power output. Mavacamten also decreased shortening in adult rat cardiac myocytes in a concentration-dependent and Ca^{2+}-independent manner (IC_{50} 0.25 µM). The reduced myocyte contractility is consistent with the mechanistic biochemical data showing that mavacamten reduces force production and thus contractility.

In vivo, mavacamten, administered orally to healthy rats at doses of 1 to 10 mg/kg, dose-dependently decreased fractional shortening (FS) and increased end-diastolic volumes (EDV) with an IC_{50} of 679 ng/mL. Mavacamten at 1-2 mg/kg preserved mean systemic blood pressures and dose-dependently decreased dP/dt_{max} with mild/moderate cardio-acceleration, while preserving left ventricular end-diastolic pressures (EDP). At 4 mg/kg, mavacamten led to marked reductions in both FS (-54%) and stroke volume (-40%), which were rescued by acute administration of either dobutamine (synthetic β-adrenoreceptor agonist) or levosimendan (phosphodiesterase-3 inhibitor). These data suggest that mavacamten's effect on cardiac performance *in vivo* occurs by a mechanism different from that of the classical inotrope agents. Similar to rats, chronic oral administration of 45 µg/kg/day to dogs produced decreases in left ventricular ejection fraction (LV EF, -11%), LV FS (-9%), and dP/dtmax (-17%), while systemic haemodynamic were maintained. In healthy dogs, mavacamten given orally at 1.5 mg/kg induced marked systolic functional depression [e.g. LV EF -28%, preload-recruitable stroke work (PRSW) -35%] and increased preload (EDV, +14%), indicating a reduction in overall myocardial power. Both EDP and the elastance at end-diastole were preserved post-treatment, in agreement with the postulated mode of action. In mice expressing pathogenic HCM mutations, oral mavacamten treatment (0.83 mg/kg/day, leading to plasma exposures between 0.70 and 2.23 µM) improved disease-related cardiac function while preserving FS.

Overall, in all three animal models, mavacamten led to reduction of cardiac contractility while preserving both systemic haemodynamic and cardiac filling pressures. As such, and in contrast to negative inotropes, mavacamten seems to improve ventricular distensibility. In addition, consistent with its direct sarcomere-targeted functional modulation, cardiac β-adrenergic receptor functions were unaffected by mavacamten treatment.

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Mavacamten (up to 30 µM) did not show cytotoxic effects in 13 different cell lines, nor significant off-target effects in a secondary pharmacodynamic screening assay on a panel of 143 different targets at 10 µM.

Mavacamten was extensively evaluated *in vitro* and *in vivo* in studies to assess effects on cardiovascular, respiratory, and central nervous system (CNS) function according to ICH S7A/B. Mavacamten administration had no noteworthy cardiorespiratory or CNS effects at doses up to 10 mg/kg in rats. In conscious dogs, no cardiovascular or respiratory effects occurred at a dose of 1 mg/kg (1.42-fold C_{max} and approx. 0.38-fold exposure in humans at therapeutic dose). Mavacamten at single oral doses of 3 and 10 mg/kg caused dose-dependent reductions in systolic and pulse arterial systemic pressures as well as concomitant increases in heart rate. Respiratory effects were limited to transient increases in respiratory rate and reduction in tidal volume at 10 mg/kg. Additionally, at 10 mg/kg an increase in QTc interval at Week 1, identified as an important potential risk, and an increased incidence of ectopic activities of ventricular origin for up to 3 weeks were observed.

5.2 Pharmacokinetics

The pharmacokinetics of mavacamten were studied after single intravenous (IV) and oral administration in mice, rats, dogs, and monkeys. Following a single IV administration, plasma mavacamten levels followed a rapid distribution and a slow clearance phase in all species. After a single oral administration, T_{max} was within 0.25-0.7 h, followed by a monoexponential decay with $T_{1/2}$ of 4.2 h, 8.2 h, 161 h, and 42.7 h in mice, rats, dogs, and monkeys, respectively. In rats, a food effect (reduced exposure) was observed, but not in dogs.

In vitro plasma protein binding of mavacamten was high in mouse, rat, dog, human, and monkey plasma (83.9%, 89.0%, 91.1%, 93.1%, and 95.1%, respectively). Mavacamten blood-to-plasma partitioning in these species was between 0.72 and 0.82, i.e. there was no preferential distribution into blood cells.

Following single or repeat oral dosing of 1 mg/kg mavacamten in rats, the distribution into liver and kidney was moderate. Tissue to plasma ratios of mavacamten for striated muscles, heart, soleus, and extensor digitorum longus was 10 (3.7 for smooth muscle). Following a single oral dose of 1 mg/kg radiolabelled mavacamten to pigmented Long Evans and non-pigmented Sprague Dawley rats, radioactivity was rapidly absorbed and was widely distributed in tissues and organs. In pigmented rats, most tissues had peak radioactivity concentrations at 0.5 h post-dose, and the highest peak concentrations were seen in myocardium, diaphragm, liver, salivary gland, skeletal muscle, and oesophagus. Mavacamten exhibited minimal to no affinity to melanin. Distribution trends in the non-pigmented rats were generally comparable to pigmented rats. No sex difference was noted and there was no obvious trend of accumulation.

The metabolic profile of mavacamten was investigated in liver microsomes and hepatocytes of mice, rats, dogs, monkeys, and humans. Mavacamten was metabolically stable in liver microsomes from all species tested. Thirteen metabolites were detected, identified and characterised across species. No human-specific metabolites were identified. CYP2C19, CYP3A4/5, and CYP2C9 contributed largely to the hepatic metabolism of mavacamten *in vitro.* Following IV administration of 1 mg/kg, mavacamten was the most abundant component in rat plasma with only minor metabolites detected systemically, which were all below 5% of the parent by AUC.

Following a single oral administration of radiolabelled mavacamten in bile duct-cannulated male rats at 1 mg/kg, excretion in faeces was the predominant route of excretion (58% of the administered radioactivity), whereas in humans, urinary excretion is the major route of elimination. The passage into milk was not studied. The recommendation for use during lactation in the Information for healthcare professionals is adequate.

5.3 Toxicology

The toxicological profile of mavacamten was evaluated in mice, rats, rabbits, and dogs. Rats and dogs were selected as the main toxicology species, based on the similarity of their pharmacological and metabolic profile to humans. The route of administration and frequency of dosing in the non-

clinical studies are consistent with the proposed clinical setting. Pivotal repeat-dose oral toxicity studies were conducted up to 26 weeks in rats at doses of 0.3, 0.6, or 1.2 mg/kg/day and 39 weeks in dogs at doses of 0.06, 0.18, 0.30, or 0.45 mg/kg/day. Exposure of rats and dogs at the NOAELs for systemic toxicity was below the clinical exposure, i.e. there are no safety margins, suggesting potential risk in the therapeutic dose range.

The main target organ for toxicity was the heart. Continued excess mavacamten pharmacology leading to cardiac dysfunction or decreased cardiac contractility were the major cause of test item-related premature deaths or euthanasia in all species. Mavacamten administration at ≥ 1.2 mg/kg/day in rats (0.64-fold human exposure) and ≥ 0.45 mg/kg/day in dogs led to mortality as a consequence of heart failure. The effects observed in other organs such as lungs, liver, and spleen were considered secondary effects of cardiac failure due to test-item-related decreased blood circulation. Mavacamten-related findings in the heart of rats at ≥ 0.6 mg/kg/day consisted of an increase in heart weight reflecting the cardiac hypertrophy noted at microscopic examination, and inflammation, myocardial degeneration, osseous metaplasia of cardiac muscles, and dilatation. The mavacamten-related microscopic heart finding of osseous/cartilaginous metaplasia noted at terminal euthanasia is considered adverse. Recovery is unlikely due to its nature (cartilage and/or bone formation) and it must be considered as a permanent effect. Similar findings to rats were noted in dogs. Cardiac dilation without heart weight change was observed at necropsy. As in rats, secondary effects in non-cardiac tissues related to insufficient cardiac function included pulmonary oedema, gall bladder oedema, pleural fluid, hepatic congestion, and centrilobular hepatocellular necrosis. Increased heart rate and slightly prolonged QT and QTc were observed by electrocardiography in the 3-month and 39-week toxicity studies without any clinical symptoms. All these findings were reversible except for the heart histopathology.

Mavacamten was negative in *in vitro* and *in vivo* genotoxicity assays according to ICH S2 (R1).

Mavacamten was not carcinogenic in rats and transgenic mice. Maximum exposure of the animals in the studies was below (rats) or 1.8-fold (mice) the systemic exposure in humans at the therapeutic dose.

Mavacamten did not affect the fertility of male or female rats or the fertility of F1 offspring of female rats dosed with mavacamten during gestation. In the embryo-fetal development studies, maternal toxicity was not observed in rats at doses up to 1.5 mg/kg/day but was in rabbits at ≥ 1.2 mg/kg/day. Mavacamten was teratogenic in both species. The exposures at the NOAELs in both rats and rabbits were below the maximum recommended human dose. In the pre- and postnatal developmental toxicity study in rats, no adverse mavacamten-related effects were observed in the dams or offspring. This is adequately reflected in the Information for healthcare professionals and the recommendations for use during pregnancy are appropriate.

The non-clinical safety specifications in the RMP adequately address the non-clinical findings and their relevance for clinical use.

Juvenile animal studies were not conducted. Mavacamten is not intended for use in a paediatric population.

Impurities are controlled according to ICH Q3A/B and ICH M7. There are no concerns about the excipients.

Based on the ERA, the risk for the environment is low.

5.4 Non-clinical conclusions

In conclusion, a comprehensive study package covering pharmacology, pharmacokinetics, and toxicology has been submitted for Camzyos (mavacamten). Although the margins of exposure are less than 1, there are no non-clinical findings that preclude the approvability of mavacamten, and the pharmacological and toxicological data support approval of Camzyos in the proposed indication. All non-clinical data relevant to safety are mentioned in the Information for healthcare professionals.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

ADME

Absorption and biopharmaceutical development
Mavacamten was classified as a BCS II substance (high permeability, low solubility). In the course of the clinical development of mavacamten, an oral suspension, two tablet formulations (campaign 1 and 2), and two capsule formulations (capsule 1 and 2) were employed. Both capsule formulations were administered in the pivotal Phase 3 study. Apart from the colour and imprint of the gelatin capsule, capsule 2 is identical to the proposed commercial formulation.

Capsule 1 and 2 were bioequivalent after fasted administration.

The administration of capsule 2 with a high-fat meal caused a 55.3% reduction of mavacamten C_{max}, an increase of the inter-individual variability of C_{max} from 28% to 56%, and a prolongation of the median t_{max} from 1.010 h to 4.010 h. There was also a slight reduction of the mavacamten AUC (12%↓) after fed administration, but the formal bioequivalence criteria were still met. Mavacamten can be administered independently of food intake.

Dose proportionality
The results of the pop PK analysis indicated a slightly more than dose-proportional increase of mavacamten exposures over the range of 2.5 mg to 15 mg. There was a 3.56-fold increase of mavacamten $C_{avg,ss}$ for a 3-fold increase of the dose from 5 mg to 15 mg.

Pharmacokinetics after multiple dosing
Mavacamten reached its steady state after 26 days of QD or BID dosing. The accumulation index calculated independently of the CYP2C19 genotype was up to 8.15-fold after BID dosing and up to 7.28-fold after QD dosing. A reliable estimate of the linearity index was not possible due to the long half-life of mavacamten.

Distribution
The mean mavacamten *in vitro* plasma protein binding was 93.1% and in a range of 0.2 µM (54.67 ng/mL) to 10 µM (2733 ng/mL) independent of the concentration. The *in vitro* blood to plasma ratio was 0.79. A comparable value of 0.705 was obtained *ex vivo* after administration of a ^{14}C-labelled mavacamten dose. Mild or moderate hepatic impairment had no effect on mavacamten *ex vivo* plasma protein binding.

Metabolism - In vitro data
Mavacamten was metabolised by CYP2C19 (74.3% fraction metabolised (fm)), CYP3A4 (18.0% fm), and CYP2C9 (7.55% fm). The CYP reaction phenotyping results suggested that the most abundant metabolite in plasma MYK-1078 (M2) was primarily formed by CYP2C19.

Metabolism & elimination - Clinical data
After administration of a single ^{14}C-labelled mavacamten dose, unchanged mavacamten accounted for 70% of the total radioactivity in plasma. Several other metabolites were detected in plasma, none of them accounting for more than 4% of the total radioactivity in plasma. The highest contribution of 3.56% was due to MYK-1078, formed by oxidation. The *in vitro* pharmacological activity of MYK-1078 was comparable to that of mavacamten.

The identification of the total radioactivity in plasma was almost complete.

The “cold” investigation of metabolites in plasma after administration of 18.5 mg mavacamten QD for 28 days showed similar results: several metabolites were identified, none of them accounting for more

than 5% of the mavacamten AUC_{0-24h}, and MYK-1078 contributing most with 2.07% of the mavacamten AUC.

Hydrolysis and oxidative N-dealkylation were minor primary biotransformation pathways, while dehydrogenation, dehydration, methylation, glucuronidation, and glycine conjugation were minor secondary biotransformation pathways of mavacamten.

After administration of a single ^{14}C-labelled mavacamten dose, 85.2% and 7.02% of the total radioactivity were exreted in urine and faeces, respectively. The total recovery within 47 days post dose was 92.2%.

The main compound excreted in urine was MYK-1078, accounting for 50.6% of the administered radioactive dose. Unchanged mavacamten accounted for 1.68% of the dose. Several other metabolites were detected, none of them accounting for more than 5% of the dose. Only 1.66% of the administered radioactive dose was not assigned to mavacamten and its metabolites.

MYK-1078 was also the main compound excreted in faeces, accounting for 1.15% of the administered radioactive dose. Unchanged mavacamten accounted for 0.816% of the dose. Several other metabolites were detected in faeces, none of them accounting for more than 1% of the dose. Only 0.856% of the administered radioactive dose was not assigned to mavacamten and its metabolites.

The half-life of mavacamten and MYK-1078 in CYP2C19 extensive metabolisers (EM) was 129 h to 159 h and 103 h, respectively. The half-life of the total radioactivity in plasma was of similar magnitude.

Special populations

The mavacamten C_{max} and AUC were comparable in healthy Japanese and Caucasian subjects of similar body weight and CYP2C19 genotype.

There was a 1.47-fold and 3.41-fold increase of mavacamten C_{max} and AUC_{inf} in CYP2C19 poor metabolizers (PM) compared to EM. The mean mavacamten half-life in PM was 571.6 h.

The findings in subjects with mild hepatic impairment (HI) were similar. There was a 1.12-fold and 3.91-fold increase of mavacamten C_{max} and AUC_{inf}, respectively, compared to the healthy control group. In subjects with moderate hepatic impairment, a 1.10-fold and1.67-fold increase of mavacamten C_{max} and AUC were observed. The mavacamten half-life was prolonged in subjects with hepatic impairment (634h in mild HI, 420 h in moderate HI).

Additional intrinsic factors, including but not limited to age, sex, race, and renal function, were investigated in a popPK analysis. The popPK dataset included seven Phase 1 studies, three Phase 2 studies and two Phase 3 studies. It included 497 subjects, of which 192 (38.6%) were healthy subjects, 54 (10.9%) were subjects with non-obstructive hypertrophic cardiomyopathy (nHCM) and 251 (50.5%) were subjects with obstructive hypertrophic cardiomyopathy (oHMC). The overall age range of the subjects was 18 to 82 years. Twenty (4.0%) of the subjects were ≥ 75 years and 88 (17.7%) were between 65 and 74 years old. The weight range was 44.9 to 160 kg. Most of the subjects (297, 59.8%) in the dataset had normal renal function and176 (35.4%) had mild renal impairment, 22 (4.4%) had moderate renal impairment. The dataset included only 1 subject with severe renal impairment and another one with end-stage renal disease. The majority of the subjects had normal hepatic function.
The distribution of CYP2C19 phenotypes in the dataset was 39.8% normal metabolisers (NM), 17.9% extensive metabolisers (EM), 19.1% rapid metabolisers (RM), 3.4% poor metabolisers (PM), 4.6% ultra rapid metabolisers (UM) with genotype *2/*17 and 3.2% UM with genotype *17/*17. The CYP2C19 genotype was missing in 11.9% of the subjects.

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The effects of body weight on clearance and volume terms, CYP2C19 genotype on mavacamten clearance and differences regarding the absorption of the oral suspension and the tablets/capsules were already implemented in the base model.

The final popPK model included additionally the following covariate relationships:

- Dose strength as a covariate of F, Ka, and lag time
- eGFR as a covariate of CL/F
- Fed/fasted status in healthy subjects on F, Ka, and lag time
- Esomeprazole and omeprazole co-administration as a covariate of CL/F
- Healthy subject status as a covariate of CL/F
- Sex as a covariate of CL/F and F

The final model described the mavacamten concentration-versus time profiles reasonably well. Of all covariates investigated, being a CYP2C19 PM had the largest impact on mavacamten exposures. The estimated 3.55-fold increase of mavacamten $C_{avg,ss}$ was in good agreement with the results of the dedicated Phase 1 study. The model predicted a 20.2% reduction of mavacamten $C_{avg,ss}$ in UM, a similar $C_{avg,ss}$ in EM and RM, and a 1.5-fold increase of $C_{avg,ss}$ in intermediate metabolisers (IM).

All other covariates resulted in less than 2-fold changes in mavacamten exposures.

The data support the dosing recommendations in special populations summarised in the Information for healthcare professionals.

Interactions

Effect of other drugs on mavacamten
In vitro data
As mentioned above, mavacamten is metabolised by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9. Mavacamten was not a substrate of P-gp or hepatic uptake transporters.

Clinical data

Perpetrator	**GMR (90% CI)**
Verapamil (moderate CYP3A4 inhibitor)	Cmax: 1.518 (1.160,1.985) AUCinf: 1.155 (0.844,1.582)
Omeprazole (weak CYP2C19 inhibitor)	Cmax: 0.99 (0.75, 1.30) AUCinf: 1.48 (1.16, 1.88)

The effects of CYP3A4 and CYP2C19 inhibitors of different strengths and strong CYP2C19/3A4 inducers on mavacamten exposures were investigated by PBPK simulations. The PBPK models had some limitations, but overall the dosing recommendations summarised in the Information for healthcare professionals were supported.

Effect of mavacamten on other drugs
In vitro Data
At concentrations up to 200 µM (54600 ng/mL), mavacamten did not directly inhibit CYP1A2, 2B6, 2C8, 2D6, or 3A4. It directly inhibited CYP2C9 with a Ki of 59.5 µM and CYP2C19 with a Ki of 46.2 µM. Using the basic model, these Ki values indicated no risk of reversible inhibition at therapeutic mavacamten exposures. However, a risk of time-dependent inhibition of CYP2C19 could not be excluded.

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At concentrations up to 15 µM, mavacamten did not induce CYP1A2. The induction of CYP2C8, 2C9, 2C19, or 3A4 at therapeutic mavacamten exposures could not be excluded.

According to the static DDI risk assessment, the inhibition of MATE1, MATE2-K, OAT1, or OAT3 was unlikely at therapeutic mavacamten exposures. This was also the case for the inhibition of P-gp, BSEP, BRCP, OATP1B1, OATP1B3, OCT1, and OCT2.

Clinical data

Victim	GMR (90% CI)
Ethinylestradiol (EE) & norethindrone (NOR) (substrates of CYP3A4 and 2C9)	EE Cmax: 1.05 (0.945, 1.16) EE AUCinf: 1.20 (1.08, 1.33) NOR Cmax: 1.14 (0.979, 1.33) NOR AUCinf: 1.12 (1.01, 1.24)
Midazolam (CYP3A4 substrate)	MID Cmax: 0.93 (0.77, 1.13) MID AUClast: 0.76 (0.61, 0.95) 1-OH MID Cmax: 1.28 (1.00, 1.65) 1-OH MID AUClast: 1.11 (0.96, 1.29)

The effect of mavacamten as a CYP inducer was further investigated by PBPK simulations.

The oral contraceptive interaction study was used for both development and verification of the ethinylestradiol model. The model predicted the effect of mavacamten on ethinylestradiol exposures reasonably well.

The midazolam model was successfully verified with published data. It described the effect of mavacamten on midazolam exposures reasonably well.

The models of the other CYP substrates investigated as victims (bupropion (CYP2B6), repaglinide (CYP2C8), tolbutamide (CYP2C9), and lansoprazole (CYP2C19)) in this analysis were also successfully verified with literature data. The model predicted no clinically relevant effect of mavacamten on these substrates in CYP2C19 EM and PM at therapeutic exposures.

The data supported the dosing recommendations summarised in the Information for healthcare professionals.

Pharmacodynamics

Secondary pharmacology (safety)
Instead of a dedicated tQT study, an exposure-response analysis was conducted. Matched data pairs of ECG measurements and measured mavacamten concentrations were included in the analysis.

QTcF was a reasonable QT correction and was therefore selected as the primary endpoint of the analysis. Mavacamten had no major impact on heart rate.

The final model was a linear mixed effects model combined with the estimation of a non-parametric placebo response for each time-point and visit of each trial to account for heterogeneity in response in the absence of measurable concentrations. The model described the data reasonably well.

In healthy subjects, a median mavacamten concentration <1152 ng/mL would be expected to maintain the mean ΔΔQTcF <10 ms. A median concentration <593 ng/mL would be expected to maintain the upper 90% CI of mean ΔΔQTcF <10 ms.

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Relationship between plasma concentration and effect

Efficacy
Based on the results of descriptive analyses, quantitative analyses of the relationship between mavacamten exposure and LVEF and LVOT were performed.

The LVEF and LVOT datasets included 331 and 272 subjects, respectively. Predicted mavacamten CAVG168h was used as the exposure measure in both analyses. It was closely correlated with the observed mavacamten trough concentrations. The covariates investigated in both analyses included the use of background beta-blockers and calcium channel blockers, baseline NYHA classification, the baseline values of the respective dependent variables, study population (nHCM or oHCM), and gender.

LVEF
The final model was a power model including baseline LVEF, study population (oHCM versus nHCM), and sex as covariates of the model intercept. Baseline LVEF was also a covariate of the model steepness parameter. Study MYK-461-005 was found to differ from other studies, and the model therefore required a Study MYK-461-005 covariate on both the steepness parameter and the power model exponent. The reason for the different exposure-response relationship in Study 005 is unknown, but is not regarded as clinically relevant. The baseline LVEF was 74%, and it was 3.24% lower for nHCM (versus oHCM) subjects and 1.40 % higher for female (versus male) subjects. While the power model described the data of Study 005, an almost linear relationship between mavacamten exposure and LVEF was found for the other studies. The final model described all data, including placebo, reasonably well.

LVOT
LVOT was used as a surrogate efficacy endpoint. Exploratory analyses indicated that the largest changes from baseline in NYHA class and pVO_2, both components of the primary endpoint of Study 005, were associated with LVOT gradients < 30 mmHg.

The final LVOT model was a decaying exponential model including baseline LVOT as a covariate of the model intercept, and slope and baseline NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) as covariates of the model intercept. The model also included a placebo effect (or background treatment effect) that accounted for a maximum of 12.3% [6.1, 18.5; 95% CI] improvement of LVOT over time. The model described the data reasonably well.

Both models (LVEF and LVOT) were used to simulate alternative titration regimens as were used in Study 005. Prior to the simulations, the models were successfully qualified by predicting the Study 005 data from the original titration regimen used in the study.

Safety
These analyses were limited to descriptive analyses.

There was no consistent exposure-response relationship in the sense of an increasing AE incidence with increasing mavacamten exposure, but AEs related to the pharmacological action of mavacamten like cardiac failure or systolic dysfunction occurred more frequently in the fourth exposure quartile.

This trend was most clearly visible for TEAEs of clinical interest. The highest incidence of these events of clinical interest was observed at mavacamten concentrations >1000 ng/mL, which triggered down-titrations of the dose in Study 005.

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6.2 Dose finding and dose recommendation

Pharmacometric aspects

The approved titration regimen is based on simulations with the final exposure-response models for LVOT and LVEF described above. The main difference to the titration employed in Study MYK-471-005 was the switch from mavacamten plasma concentrations to LVOT and LVEF to guide the mavacamten dose titration.

The reasons for using echocardiographic parameters rather than mavacamten plasma concentrations to guide mavacamten dose titration were the instant availability of the results and the better correlation of the LVOT gradient with the clinical outcome as described above. The results of the exposure-response analyses indicated an indirect relationship between mavacamten plasma concentrations and clinical efficacy. The mavacamten plasma concentrations were directly related to the LVOT gradient and LVEF, which were associated with NYHA class and pVO2, but there was no consistent direct relationship between mavacamten concentrations and the clinical endpoints.

The target of the dose titration was to maintain LVEF ≥ 50% and LVOT ≥ 20 mmHg.

The starting dose of 5 mg QD should be administered independently of the CYP2C19 genotype despite the higher mavacamten exposures in CYP2C19 PM.

6.3 Efficacy

The efficacy of was demonstrated in a multicentre, international, placebo-controlled, randomised 2-arm study in 251 patients with symptomatic oHCM that required treatment.

Patients with a significant LVOT gradient ≥50 mmHg at rest, during Valsalva, or after exercise and symptoms (NYHA Class II or III) were randomised 1:1 to receive mavacamten (n = 123) or placebo (n = 128) once daily for 30 weeks. An 8-week follow-up period was chosen to provide sufficient time for drug washout based on 4 - 5 times the half-life. Randomisation was stratified by NYHA class, current beta-blocker therapy, type of ergometry (treadmill or bicycle), and consent for a cardiac magnetic resonance imaging sub-study.

Therapy was initiated with mavacamten 5 mg or placebo once daily, followed by blinded dose adjustment defined in the study protocol. The dose could be down-titrated to a lowest dose of 2.5 mg or up-titrated to a maximum dose of 15 mg once daily based on LVEF and LVOT Valsalva gradient, along with mavacamten plasma concentrations.

Patient demographics and baseline criteria were similar in both treatment groups. At baseline, the majority of patients were NYHA Class II (72.9%) and NYHA Class III (27.1%). Left ventricles were hypertrophic (mean LV maximum wall thickness 20 mm) and function was hypercontractile (mean LVEF 74%), with progressive obstruction from rest to provocation (mean resting LVOT gradients approximately 50 mmHg and increasing to approximately 85 mmHg after exercise).

The composite functional primary endpoint was defined as achieving either: 1) an improvement in pVO_2 by ≥1.5 mL/kg/min and improvement of ≥1 NYHA class, or 2) an improvement in pVO_2 by ≥3.0 mL/kg/min and no worsening of NYHA class at Week 30.

37% of patients in the mavacamten group achieved the primary endpoint compared with 17% in the placebo group, p = 0.0005. The proportion of patients who achieved both an increase of ≥3 mL/kg/min in pVO_2 and an improvement of ≥1 NYHA class was greater in the mavacamten group compared with the placebo group (20.3% vs. 7.8%). The primary composite functional endpoint and all secondary endpoints were analysed by predefined subgroups. Mavacamten showed consistent benefit for the primary composite functional endpoint and all secondary endpoints across a diverse range of patients

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with respect to demographic characteristics, including age, race, sex, and BMI. The therapeutic effects of mavacamten were also observed across baseline disease characteristics, which included LVEF, NYHA class, NT proBNP levels, and HCM genotype.

6.4 Safety

In the pivotal phase 3 study throughout the duration of 30 weeks, overall incidences of AEs, Grade ≥3 AEs, SAEs, and cardiac AEs, including atrial fibrillation and ventricular tachycardia, were comparable for patients treated with mavacamten or placebo. Most serious and non-serious events reported were outcomes or symptoms of the underlying disease or were common events or conditions in the population.
The incidence of AEs in the mavacamten group leading to permanent treatment discontinuation was low (2 of all mavacamten-treated patients, 1.6%). Across the integrated analyses with all mavacamten-treated patients and including data from long-term extension studies with extended exposure to mavacamten, the incidence of AEs leading to permanent treatment discontinuation remained low (3.2%, 10 patients).
Safety was consistent overall across subgroups including mavacamten-treated patients with baseline beta-blocker use. There were no meaningful differences in severe or serious events (Grade ≥3 AEs or SAEs, respectively) for patients stratified by baseline beta-blocker use. Dizziness was the most frequently reported event in mavacamten-treated patients.

6.5 Final clinical and clinical pharmacology benefit risk assessment

Cardiomyopathies are a heterogeneous group of heart disorders characterised by structural and functional abnormalities of the myocardium. Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium (60-70%). 2 subclasses of HCM are distinguished: obstructive HCM (oHCM) and non-obstructive HCM (nHCM). The proportion of subjects with HCM who have oHCM ranges from 22% to 70%. There are limited pharmacological and surgical treatment options for the chronic and progressive symptoms of oHCM, leaving an unmet medical need for a targeted therapy of oHCM.

Beneficial effects and respective uncertainties
Mavacamten can be administered independently of food intake. Its exposures increased approximately dose proportionally across the relevant dose range. There was no evidence of major non-linearities in mavacamten PK. There are no relevant mavacamten metabolites and the conversion to the inactive enantiomer MYK-460 is minimal. As the mavacamten dose is individually titrated based on echocardiographic parameters, no further dose adjustments for age, hepatic function, renal function, or CYP2C19 genotype are required. However, the proposed titration regimen was not investigated in clinical studies and is entirely simulation-based. The interaction potential of mavacamten as a perpetrator appears to be low. There was a direct relationship between mavacamten plasma concentrations and both LVOT gradient and LVEF. Both decreased with increasing mavacamten concentrations. The exposure-response models, which were used to simulate the proposed titration regimen, described the data reasonably well.

The efficacy of mavacamten was demonstrated in a multicentre, international, placebo-controlled, randomised 2-arm study over 30 weeks in 251 patients with symptomatic oHCM that required treatment. 37% of patients in the mavacamten group achieved the primary endpoint compared with 17% in the placebo group, p = 0.0005. The proportion of patients who achieved both an increase of ≥3 mL/kg/min in pVO_2 and an improvement of ≥1 NYHA class was greater in the mavacamten group compared with the placebo group (20.3% vs. 7.8%). Outcomes for oHCM-related secondary and

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exploratory endpoints were consistent with these findings. The beneficial effect of mavacamten was principally consistent across subgroups.

Evidence is limited to the clinical study described above and a follow-up study over 8 weeks.

Unfavourable effects and respective uncertainties

The half-life of mavacamten is quite long. Consequently, it takes time for dose adjustments to affect mavacamten exposures. The CYP2C19 genotype has a substantial effect on mavacamten exposures. There are no PK data available in subjects with severe hepatic or renal impairment.
There was no direct relationship between mavacamten plasma concentrations and the primary clinical efficacy endpoint. There was no consistent exposure-response relationship in the sense of increasing AE incidence with increasing mavacamten exposure, but AEs related to the pharmacological action of mavacamten like cardiac failure or systolic dysfunction occurred more frequently in the fourth exposure quartile.
Dizziness was the most frequently reported event in mavacamten-treated patients. There were no meaningful differences in severe or serious events (Grade ≥3 AEs or SAEs, respectively) for patients stratified by baseline beta-blocker use.

Benefit-risk balance

There are no major clinical pharmacology issues for mavacamten. From a clinical pharmacology point of view, the proposed titration regimen based on echocardiographic parameters rather than mavacamten plasma concentrations is reasonable.
Clinical data showed a beneficial effect of mavacamten in the treatment of oHCM over 30 weeks and an acceptable safety profile.

Overall, treatment of oHCM with mavacamten should be carried out by cardiologists experienced in oHCM therapy.
The benefit-risk ratio for mavacamten for the treatment of oHCM has been assessed as positive.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Camzyos was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

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IMPORTANT WARNING on the use of **CAMZYOS: RISK OF HEART FAILURE**
Camzyos can cause heart failure due to systolic dysfunction (Warnings and Precautions).
Echocardiogram assessments of left ventricular ejection fraction (LVEF) required before and during Camzyos use (Dosage/Administration).
Initiation in patients with LVEF <55% not recommended.
Interrupt if LVEF <50% or if worsening clinical status (Dosage/Administration, Warnings and Precautions).
Caution is required when administrating certain CYP450 inhibitors and inducers in patients taking Camzyos because of an increased risk of heart failure (Dosage/Administration, Warnings and Precautions, Interactions).

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Camzyos®

Composition

Active substances

Mavacamten.

Excipients

Colloidal hydrated silica, mannitol, hypromellose, croscarmellose sodium (manufactured from genetically modified cotton), magnesium stearate.
Capsule shell: gelatin, titanium dioxide, black iron oxide (hard capsules 2.5 mg and 15 mg), red iron oxide (hard capsules 2.5 mg and 10 mg), yellow iron oxide (hard capsules 5 mg).
Printing ink: black iron oxide, shellac, propylene glycol, concentrated ammonia solution, potassium hydroxide.
One hard capsule contains 0.5 mg (hard capsules 2.5 mg), 1.1 mg (hard capsule 5 mg), 0.8 mg (hard capsules 10 mg) or 1.3 mg (hard capsule 15 mg) sodium.

Pharmaceutical form and active substance quantity per unit

Hard capsules.
Hard capsules of 2.5 mg: 1 hard capsule (light purple/white with imprint "2.5 mg" and "Mava") contains 2.5 mg of mavacamten.
Hard capsules of 5 mg: 1 hard capsule (yellow/white with imprint "5 mg" and "Mava") contains 5 mg of mavacamten.
Hard capsules of 10 mg: 1 hard capsule (pink/white with imprint "10 mg" and "Mava") contains 10 mg of mavacamten.
Hard capsules of 15 mg: 1 hard capsule (grey/white with imprint "15 mg" and "Mava") contains 15 mg of mavacamten.

Indications/Uses

Camzyos is indicated for the treatment of adult patients with symptomatic (NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) to improve functional capacity and associated symptoms (see “Properties/Effects”).

Dosage/Administration

Therapy with mavacamten should be initiated and monitored by a physician familiar with the treatment of patients with cardiomyopathy.

Testing prior to initiation

Before treatment initiation, patients’ LVEF should be assessed by echocardiography (see “Warnings and precautions”). If LVEF is < 55%, treatment should not be initiated.

Initiation, maintenance and interruption of treatment

The recommended starting dose is 5 mg orally once daily with or without food; allowable subsequent doses with titration are 2.5, 5, 10, or 15 mg once daily. The maximum dose is 15 mg once daily.

Initiation or up-titration of Camzyos in patients with LVEF <55% is not recommended.

Patients may develop heart failure while taking Camzyos. Regular LVEF and Valsalva left ventricular outflow tract (LVOT) gradient assessment is required for careful titration to achieve an appropriate target Valsalva LVOT gradient, while maintaining LVEF ≥50% and avoiding heart failure symptoms (see Figure 1 and Figure 2).

When initiating or titrating Camzyos, first consider LVEF then consider the Valsalva LVOT gradient and patient clinical status to guide appropriate Camzyos dosing. Follow the algorithms for initiation (Figure 1) and maintenance (Figure 2) for appropriate Camzyos dosing and monitoring schedules.

If LVEF <50% while taking Camzyos, interrupt treatment. Follow the algorithm for interruption (Figure 3) for guidance on interrupting, restarting, or discontinuing Camzyos. If interrupted at 2.5 mg, either restart the treatment at 2.5 mg or discontinue.

Figure 1. Initiation Phase

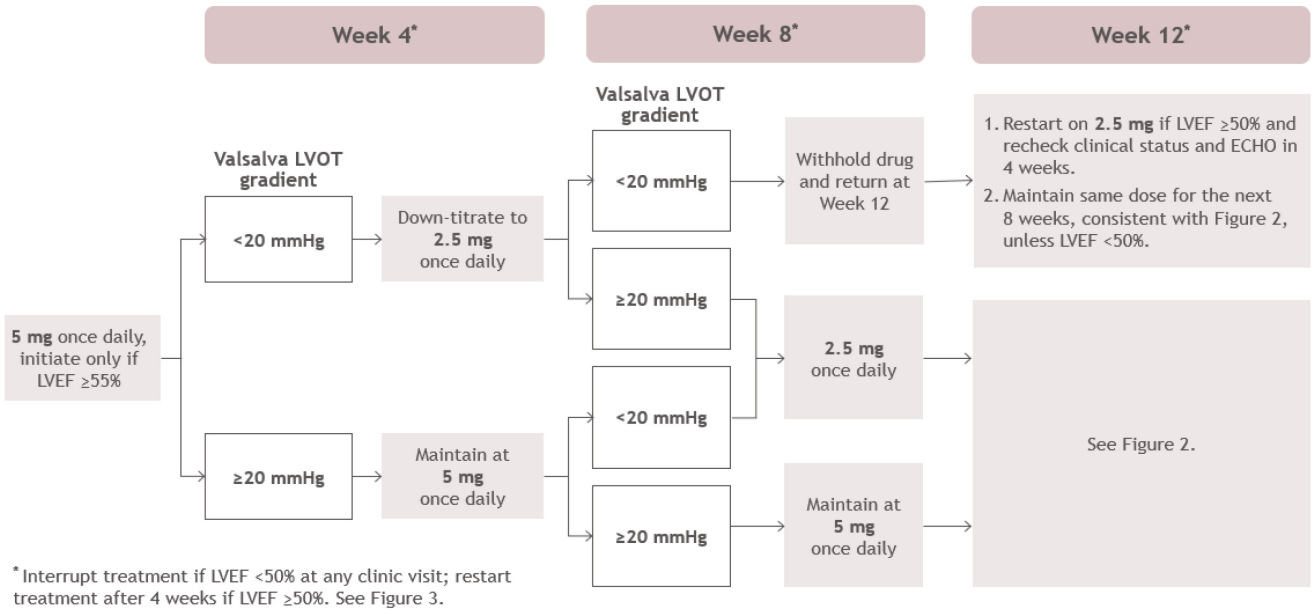
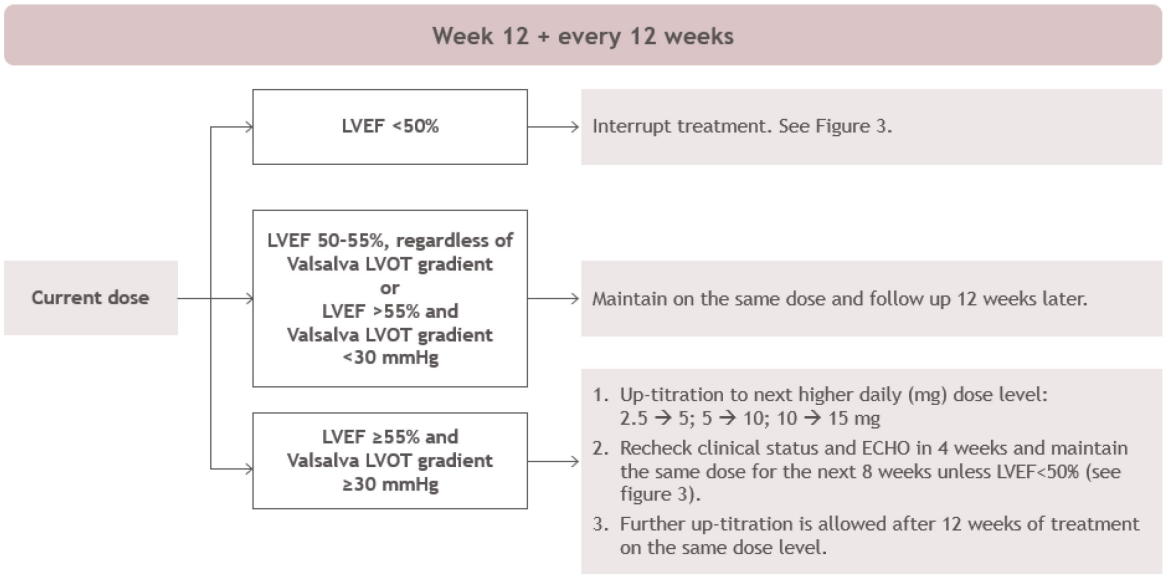


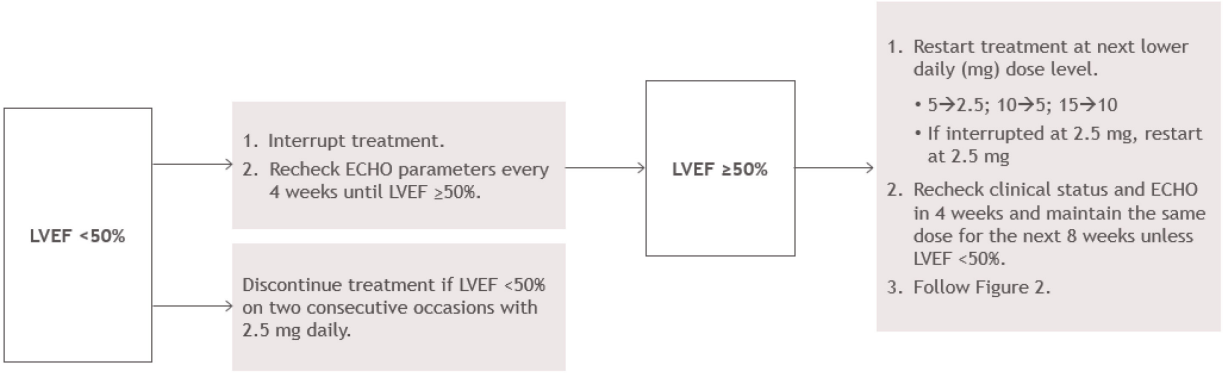
Figure 2. Maintenance Phase



Dose increases should not occur more frequently than every 12 weeks. Following any dose increase, LVOT gradient with Valsalva manoeuvre and LVEF should be assessed after 4 weeks, and then the patient should return 8 weeks later (then resume 12-weekly visits). In patients experiencing an intercurrent illness such as infections or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) which may impair systolic function, dose increases are not recommended.

Consideration should be given to discontinuing treatment in patients who have shown no response (e.g., no improvement in symptoms, quality of life, exercise capacity, LVOT gradient) after 4-6 months on the maximum tolerated dose.

Figure 3. Treatment interruption at any clinic visit if LVEF <50%



Treatment monitoring

Patients should be regularly monitored for symptoms of obstructive hypertrophic cardiomyopathy (oHCM), for left ventricular outflow tract (LVOT) gradient with Valsalva manoeuvre and for left ventricular ejection fraction (LVEF) using echocardiogram assessments.

Once an individualised maintenance dose is achieved, patients should be assessed every 12 weeks. If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50%.

If clinical status changes or in patients with a serious intercurrent illness such as infections or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia), LVEF assessment is recommended (see section "Warnings and precautions").

Dose modification with concomitant medicinal products

Initiate mavacamten at the recommended starting dosage of 5 mg orally once daily in patients who are on stable therapy with a CYP2C19 or CYP3A4 inhibitor, or with a CYP2C19 or CYP3A4 inducer.

It is recommended that patients on concomitant treatment with any CYP2C19 or a strong CYP3A4 inhibitor, or with a strong CYP2C19 or a strong CYP3A4 inducer, follow the steps shown in Table 1.

Table 1: Dose modification with concomitant medicinal products

Concomitant medicinal product	Dosage modification / monitoring
Inhibitors	
• Initiation or dose increase of: o strong CYP2C19 inhibitor	• Decrease mavacamten by one dose level • Monitor LVEF 4 weeks later, and subsequently resume the patient's monitoring and titration schedule
• Initiation or dose increase of: o moderate or weak CYP2C19 inhibitor o strong CYP3A4 inhibitor	• Consider additional monitoring of LVEF o Adjust mavacamten dose based on clinical assessment
• Discontinuation or dose decrease of: o strong CYP2C19 inhibitor o moderate or weak CYP2C19 inhibitor o strong CYP3A4 inhibitor	• Consider additional monitoring after 4 weeks • Adjust mavacamten dose based on clinical assessment
Inducers	

• Initiation or dose increase of: o strong CYP2C19 inducer o strong CYP3A4 inducer	• Consider additional monitoring after 4 weeks • Adjust mavacamten dose based on clinical assessment
• Discontinuation or dose decrease of: o strong CYP2C19 inducer o strong CYP3A4 inducer	• Monitor LVEF 4 weeks later and subsequently resume the patient's monitoring and titration schedule

Missed or delayed doses

If a dose is missed, it should be taken as soon as possible, and the next scheduled dose should be taken at the usual time the following day. Two doses should not be taken on the same day.

Elderly patients

No dose adjustments are required for patients aged 65 years and older (see "Pharmacokinetics").

Patients with renal disorders

No dose adjustment is required for patients with mild (estimated glomerular filtration rate [eGFR] 60-89 mL/min/1.73 m^2) to moderate (eGFR 30-59 mL/min/1.73 m^2) renal impairment. Caution should be used in patients with severe (eGFR < 30 mL/min/1.73 m^2) renal impairment, as Camzyos has not been studied in this population (see "Pharmacokinetics").

Patients with hepatic disorders

No dose adjustment is required for patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment. Caution should be used in patients with severe (Child-Pugh class C) hepatic impairment, as Camzyos has not been studied in this population (see "Pharmacokinetics").

Children and adolescents

The safety and efficacy of Camzyos in children and adolescents below 18 years have not been established. No data are available.

Mode of administration

For oral use.

Camzyos should be taken once daily with or without food. The capsule should be swallowed whole with water.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.
- Pregnancy

Warnings and precautions

Heart failure due to systolic dysfunction

Mavacamten reduces LVEF and may cause heart failure due to systolic dysfunction defined as symptomatic LVEF < 50%. Patients who experience a serious intercurrent illness (e.g. serious infection) or arrhythmia (e.g. atrial fibrillation or other uncontrolled tachyarrhythmia) may be at greater risk of developing systolic dysfunction and heart failure (see “Undesirable effects”). Assess the patient’s clinical status and LVEF prior to and regularly during treatment and adjust the CAMZYOS dose accordingly (see “Dosage/Administration”). New or worsening dyspnoea, chest pain, fatigue, palpitations, leg oedema or elevations in N-terminal (NT)-pro hormone b-type natriuretic peptide (NT-proBNP) may be signs and symptoms of systolic dysfunction and should prompt an evaluation of cardiac function.
Asymptomatic LVEF reduction, intercurrent illnesses, and arrhythmias require additional dosing considerations (see “Dosage/Administration”).
LVEF should be measured prior to initiating treatment and closely monitored thereafter. Treatment interruption may be necessary to ensure that LVEF remains ≥ 50%. Initiation of Camzyos in patients with LVEF <55% is not recommended (see “Dosage/Administration”).

Heart failure risk or loss of response to mavacamten due to drug-drug interactions

Mavacamten is primarily metabolised by P450 (CYP) 2C19 and CYP3A4 which may lead to the following drug interactions:

- Starting or increasing the dose of any CYP2C19 inhibitor or a strong CYP3A4 inhibitor may increase risk of heart failure due to systolic dysfunction.
- Stopping or decreasing dose of any CYP2C19 inhibitor or a strong CYP3A4 inhibitor may lead to a loss of therapeutic response to mavacamten.
- Starting a strong CYP2C19 or a strong CYP3A4 inducer may lead to a loss of therapeutic response to mavacamten.
- Stopping a strong CYP2C19 or a strong CYP3A4 inducer may increase risk of heart failure due to systolic dysfunction.

Prior to and during treatment, the potential for drug interactions of other drugs to be co-administered with mavacamten, including over the counter medications (such as omeprazole, weak CYP2C19 inhibitor), should be considered. Dose adjustment of mavacamten and/or close monitoring may be required in patients initiating or discontinuing treatment with, or changing the dose of, any CYP2C19 inhibitor or a strong CYP3A4 inhibitor or strong inducers of CYP2C19 or CYP3A4 (see “Dosage/Administration”). Intermittent administration of these medicines is not recommended (see “Interactions”).

Mavacamten monotherapy

Safety and efficacy data of monotherapy with mavacamten (8.0%) are limited (see clinical efficacy).

Concomitant use of negative inotropes

The safety of concomitant use of mavacamten with disopyramide, or use of mavacamten in patients taking beta blockers in combination with verapamil or diltiazem has not yet been established. Therefore, patients should be closely monitored when taking these concomitant medications (see “Interactions”).

Embryo-foetal toxicity

Based on animal studies, mavacamten may cause embryo-foetal harm when administered to a pregnant woman (see “Preclinical data”). Camzyos is contraindicated during pregnancy. Women of childbearing potential must use highly effective contraception during and at least 4 months after treatment (see “Pregnancy, lactation”).

Potential risk groups

No data are available for the use of mavacamten in patients with NYHA Class IV, and therefore, the treatment with mavacamten is not recommended in this oHCM patient subpopulation.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially "sodium-free".

Interactions

Effect of other medicinal products on mavacamten

Mavacamten is primarily metabolised by CYP 2C19 and to a lesser extent by CYP 3A4. Any CYP 2C19 inhibitors/inducers or strong CYP 3A4 inhibitors/inducers may thus affect the clearance of mavacamten and increase/decrease mavacamten plasma concentration (see “Warnings and precautions”).

CYP 2C19 and CYP 3A4 inhibitors

Coadministration of mavacamten with a weak CYP 2C19 inhibitor (omeprazole) resulted in a 1.48-fold (90% CI: 1.16, 1.88) increase in mavacamten AUC_{inf} with no effect on C_{max} (geometric mean ratio (GMR) 0.99 (90% CI: 0.75, 1.30)).

At initiation, discontinuation or dose adjustment of concomitant use with a strong CYP2C19 inhibitor (including, but not limited to, fluoxetine, fluconazole, fluvoxamine), mavacamten dose adjustment and/or additional clinical assessments are recommended (see “Dosage/Administration”).

At initiation, discontinuation or dose adjustment of concomitant use with a moderate or a weak CYP2C19 inhibitor (including, but not limited to, omeprazole, esomeprazole, voriconazole) or a strong CYP3A4 inhibitor (including, but not limited to, clarithromycin, ketoconazole, posaconazole, voriconazole, ritonavir, cobicistat, telaprevir, grapefruit juice), mavacamten dose adjustment and/or additional clinical assessments should be considered (see “Dosage/Administration”).

Coadministration of mavacamten with a moderate CYP 3A4 inhibitor (verapamil) resulted in a 1.16-fold (90% CI: 0.844, 1.58) and 1.52-fold (90% CI: 1.16, 1.99) increase in mavacamten AUC_{inf} and C_{max}, respectively. These changes were not considered clinically significant.

Intermittent administration of any CYP 2C19 inhibitor (such as omeprazole) or strong CYP 3A4 inhibitor is not recommended (see “Warnings and precautions”).

CYP 2C19 and CYP 3A4 inducers

Coadministration of mavacamten with any CYP 2C19 or a strong CYP 3A4 inducer (including, but not limited to, rifampicin, enzalutamide, apalutamide, phenytoin, mitotane, dabrafenib, carbamazepine, St. John’s wort) may result in a decrease in mavacamten plasma concentration. When discontinuing or reducing the dose of concomitant treatment with a strong CYP2C19 or CYP3A4 inducer, additional clinical assessments are recommended. When initiating or increasing the dose of a strong inducer,

mavacamten dose adjustment and/or clinical assessments should be considered (see "Dosage/Administration").

Intermittent administration of a strong CYP 2C19 inducer or a strong CYP 3A4 inducer is not recommended (see "Warnings and precautions").

Effect of mavacamten on other medicinal products

CYP 3A4 substrates

Coadministration of a 16-day course of mavacamten resulted in a decrease in midazolam plasma concentration (AUC_{inf} GMR 0.87 (90% CI: 0.68, 1.10) and C_{max} GMR 0.93; (90% CI: 0.77, 1.13)). This change was not considered clinically significant. Coadministration of a 17-day course of mavacamten did not decrease the exposure to ethinyl oestradiol (AUC_{inf} GMR 1.20 (90% CI: 1.08, 1.33) and C_{max} GMR 1.05 (90% CI: 0.945, 1.16)) and norethindrone (AUC_{inf} GMR 1.12 (90% CI: 1.01, 1.24) and C_{max} GMR 1.14 (90% CI: 0.979, 1.33)), which are the components of typical oral contraceptives and substrates for CYP 3A4.

Effect of mavacamten on other CYP substrates

Based on *in vitro* data, mavacamten is not an inhibitor of CYP 1A2, 2B6, 2C8, 2D6, 2C9, 2C19, or 3A4 at clinically relevant concentrations.

Effect of mavacamten on transporters

In vitro data indicate that mavacamten is not an inhibitor of major efflux transporters (P-gp, BCRP, BSEP, MATE1, or MATE2-K) or major uptake transporters (organic anion transporting polypeptides [OATPs], organic cation transporters [OCTs], or organic anion transporters [OATs]) at clinically relevant concentrations.

Substances reducing cardiac contractility

In the EXPLORER-HCM study, 119 of 123 patients in the mavacamten arm received concomitant treatment with either beta blockers, verapamil, or diltiazem (see section "Properties/Effects"). There is limited information available on the potential for a pharmacodynamic (PD) interaction between mavacamten and other substances that also reduce cardiac contractility. If treatment with a new negative inotrope is initiated, or if the dose of a negative inotrope is increased, in a patient receiving mavacamten, close medical supervision with monitoring of LVEF should be provided until a stable dose and clinical response have been achieved (see section "Warnings and precautions").

Pregnancy, lactation

Women of childbearing potential / Contraception in females

Women of childbearing potential have to use effective contraception during and at least 4 months after treatment. In women of childbearing potential, the pregnancy status must be checked prior to treatment and considered throughout treatment.

Pregnancy

There are no data from the use of mavacamten in pregnant women. Studies in animals have shown reproductive toxicity (see section “Preclinical data”). Mavacamten is suspected to cause embryo-foetal toxicity when administered during pregnancy. Camzyos is contraindicated during pregnancy (see “Contraindications”). If a patient becomes pregnant, mavacamten must be discontinued.

Breast-feeding

It is unknown whether mavacamten or its metabolites are excreted in human milk. Because of the unknown adverse effects of mavacamten in breastfed newborns/infants, Camzyos must not be used during breast-feeding.

Fertility

No clinical data on fertility in humans are available. Studies in animals showed that mavacamten had no effect on male or female fertility (see section “Preclinical data”).

Effects on ability to drive and use machines

Mavacamten may have minor influence on the ability to drive or use machines. Dizziness may occur following administration of mavacamten. Patients should be advised not to drive or use machines if they experience dizziness.

Undesirable effects

The safety of Camzyos was evaluated in EXPLORER-HCM, a Phase 3, double-blind, randomized, placebo-controlled trial. Of the 251 oHCM adult patients in this trial, 123 patients were treated with a daily dose of either 2.5 mg, 5 mg, 10 mg or 15 mg of mavacamten and 128 were treated with placebo. Mavacamten-treated patients received a median duration of exposure of 30.4 weeks (range: 1.6 to 40.3 weeks).

There were no adverse reactions leading to discontinuation of treatment. Two patients out of 123 (1.6%) in the mavacamten group and no patients (0%) in the placebo group discontinued trial drug. In the mavacamten group, the two adverse events leading to discontinuation were syncope (0.8%) and atrial fibrillation (0.8%) in one patient each.

List of adverse reactions

The adverse drug reactions (ADRs) are listed according to system organ class in MedDRA. Within each system organ class, the ADRs are presented in order of decreasing frequency and seriousness. In addition, the corresponding frequency category for each ADR is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Nervous system disorders

very common: dizziness (21.1%).

Cardiac disorders

common: heart failure, systolic dysfunction (defined as LVEF < 50% with or without symptoms).

Description of specific adverse reactions and additional information

Systolic dysfunction and heart failure

In the study, 7 patients (6%) in the mavacamten arm and 2 patients (2%) in the placebo arm experienced reversible reductions in LVEF < 50% (median 48%: range 35-49%) while on treatment. None of the 7 patients receiving mavacamten had systolic dysfunction leading to heart failure. In 3 of the 7 mavacamten patients and in 1 of the 2 placebo patients, these reductions were observed without other clinical manifestations (e.g., symptoms). In all 7 patients treated with mavacamten, LVEF recovered following interruption of mavacamten and they completed the study (see “Warnings and precautions”).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Human experience of overdose with mavacamten is limited. Mavacamten has been given as a single dose of up to 144 mg in patients with HCM. There was one serious adverse reaction of vasovagal reaction, hypotension, and asystole lasting 38 seconds reported at that dose. In healthy subjects, doses of up to 25 mg have been administered for up to 25 days. Three out of 8 participants treated at the 25 mg dose level experienced 20% or greater reductions in LVEF. Systolic dysfunction is the most likely result of overdose of mavacamten.

If warranted, treatment of overdose with mavacamten consists of discontinuation of mavacamten treatment as well as medically supportive measures to maintain hemodynamic status (e.g. initiation of inotropic support with adrenergic agents), including close monitoring of vital signs and LVEF and management of the clinical status of the patient. Early administration of activated charcoal may be considered in case of mavacamten overdose to reduce absorption. This recommendation is based on standard treatment of medicinal product overdose, as the use of activated charcoal to reduce absorption of mavacamten has not been specifically studied.

Properties/Effects

ATC code

C01EB24
Pharmacotherapeutic group: Cardiac therapy, Other cardiac preparations.

Mechanism of action

Mavacamten is a selective, allosteric, and reversible cardiac myosin inhibitor. Mavacamten modulates the number of myosin heads that can enter power-generating states, thus reducing (or in HCM normalizing) the probability of force-producing systolic and residual diastolic cross-bridge formation. Mavacamten also shifts the overall myosin population towards an energy-sparing, but recruitable, super-relaxed state. Excess cross-bridge formation and dysregulation of the super-relaxed state of myosin are mechanistic hallmarks of HCM, which can result in hyper-contractility, impaired relaxation, excess energy consumption, and myocardial wall stress. In HCM patients, cardiac myosin inhibition with mavacamten normalises contractility, reduces dynamic LVOT obstruction, and improves cardiac filling pressures and biomarkers of cardiac stress, improving symptoms and exercise capacity.

Pharmacodynamics

LVEF

A reduction in ejection fraction is expected with mavacamten treatment. In the EXPLORER-HCM study, mean (SD) resting LVEF was 74% (6) at baseline in both treatment arms. Consistent with the mechanism of action of mavacamten, reductions in mean (SD) absolute change from baseline in LVEF was -4% (8) in the mavacamten arm and 0% (7) in the placebo arm over the 30-week treatment period. At Week 38, following an 8-week interruption of study drug, mean LVEF was similar to baseline for both treatment arms.

LVOT obstruction

In the EXPLORER-HCM study, patients achieved reductions in mean resting and provoked (Valsalva) LVOT gradient by Week 4 which were sustained throughout the 30 week study duration. At Week 30, the mean (SD) change from baseline in resting and Valsalva LVOT gradients were -39 (95% CI: -44.0, -33.2) mmHg and -49 (95% CI: -55.4, -43.0) mmHg, respectively, for the mavacamten arm and -6 (95% CI: -10.5, -0.5) mmHg and -12 (95% CI: -17.6, -6.6) mmHg, respectively, for the placebo arm. At Week 38, following 8 weeks of study-drug washout, mean LVEF and LVOT gradients were similar to baseline for both treatment arms.

Other cardiac measurements

In the EXPLORER-HCM study, at Week 30 the reduction in NT-proBNP from baseline after mavacamten treatment was 80% greater than for placebo. Further reductions in other measurements including left ventricular mass index (LVMI) and left atrial volume index (LAVI) were observed compared to placebo.

Cardiac electrophysiology

In HCM, the QT interval may be intrinsically prolonged due to the underlying disease, in association with ventricular pacing, or in association with medicinal products with potential for QT prolongation commonly used in HCM population. In the EXPLORER-HCM study, there was no evidence of QTc prolongation or an increase in clinical events suggestive of ventricular arrhythmias (e.g. sudden deaths, syncope or seizures) in the mavacamten arm compared to placebo (see “Preclinical Data”). There is limited experience on coadministration of mavacamten with QT prolonging medicinal products or in patients with potassium channel variants resulting in a long QT interval.

In contrast to data observed in HCM patients but consistent with nonclinical findings in healthy hearts, in an exposure response analysis based on clinical studies in healthy subjects sustained exposure to mavacamten at supratherapeutic levels leading to marked depression of systolic function was associated with QTc prolongation (< 20 ms). No acute QTc changes have been observed at comparable (or higher) exposures after single doses. In healthy subjects, a median concentration

<1152 ng/mL would be expected to maintain the mean ΔΔQTcF <10 ms. A median concentration <593 ng/mL would be expected to not exceed the upper limit of the 90% CI of mean ΔΔQTcF <10 ms.

Clinical efficacy

The efficacy of mavacamten was evaluated in a double-blind, randomised, placebo-controlled, parallel-arm, multicentre, international Phase 3 study (EXPLORER-HCM) enrolling 251 adult patients with symptomatic NYHA class II and III oHCM, LVEF ≥ 55%, and LVOT peak gradient ≥ 50 mmHg at rest or with provocation. The majority of patients received background HCM treatment for a total of 96% in the mavacamten arm (beta blockers 76%, calcium channel blockers 20%) and of 87% in the placebo arm (beta blockers 74%, calcium channel blockers 13%).

Patients were randomised in a 1:1 ratio to receive either a starting dose of 5 mg of mavacamten (123 patients) or matching placebo (128 patients) once daily for 30 weeks. The dose was periodically adjusted to optimise patients' response (decrease in LVOT gradient with Valsalva manoeuvre), maintain LVEF ≥ 50%, and was further informed by plasma concentrations of mavacamten.
Within the dose range of 2.5 mg to 15 mg, a total of 81% (100/123) of patients were receiving either the 5 mg or 10 mg dose at the end of the treatment period, with 49% (60/123) receiving the 5 mg dose. During the study, 3 patients on mavacamten had LVEF < 50% prior to the Week 30 visit and temporarily interrupted their dose; 2 patients resumed treatment at the same dose and 1 patient had the dose reduced from 10 mg to 5 mg.

Treatment assignment was stratified by baseline disease severity NYHA functional class (II or III), current treatment with beta blockers (yes or no), and type of ergometer (treadmill or exercise bicycle) used for assessment of peak oxygen consumption (pVO_2). Patients on background dual treatment with beta blocker and calcium channel blocker treatment or disopyramide or ranolazine were excluded. Patients with a known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy, were also excluded.

Primary endpoint

The primary endpoint was comprised of a composite of change at Week 30 in exercise capacity measured by pVO_2 and symptoms measured by NYHA functional classification, defined as an improvement of pVO_2 by ≥ 1.5 mL/kg/min and an improvement in NYHA class by at least 1 OR an improvement of pVO_2 by ≥ 3.0 mL/kg/min and no worsening in NYHA class.

A greater proportion of patients met the primary endpoint at Week 30 in the mavacamten arm compared to the placebo arm (36.6% *versus* 17.2%, respectively, p = 0.0005) (see Table 2).

Table 2: Analysis of the primary composite endpoint

	Mavacamten N = 123	**Placebo N = 128**
Patients achieving primary endpoint at Week 30, n (%)	45 (37%)	22 (17%)
Treatment difference (95% CI)	19 (8.67, 30.13)	
p-value	0.0005	
Patients with change from baseline in pVO_2 ≥ 1.5 mL/kg/min and improvement in NYHA class ≥ 1 at Week 30, n (%)	41 (33%)	18 (14%)
Treatment difference (95% CI)	19 (8.99, 29.55)	
Patients with change from baseline in pVO_2 ≥ 3.0 mL/kg/min and no worsening in NYHA class at Week 30, n (%)	29 (24%)	14 (11%)
Treatment difference (95% CI)	13 (3.39, 21.89)	

A range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. Results of the primary analysis consistently favoured mavacamten across all subgroups analysed.

Secondary endpoints

The treatment effects of mavacamten on LVOT obstruction, functional capacity, and health status were assessed by change from baseline through Week 30 in post-exercise LVOT peak gradient, change from baseline through Week 30 in pVO_2, proportion of patients with improvement in NYHA class, change from baseline through Week 30 in Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) clinical summary score (CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) shortness of breath (SoB) domain score. At Week 30, patients receiving mavacamten had statistically significant improvement compared to placebo arm across all secondary endpoints.

Cardiovascular mortality

The effect of mavacamten on cardiovascular mortality has not been determined.

Elderly patients

Clinical studies of mavacamten included 95 patients aged 65 years and older; 95/263 (36.1%) patients dosed with mavacamten were 65 years of age or older, and 17/263 (6.5%) were aged 75 years or older. Safety, efficacy, and pharmacokinetics were consistent between elderly patients (≥ 65 years) and younger patients (18 to < 65 years) (see “Pharmacokinetics”).

Pharmacokinetics

Absorption

Mavacamten is readily absorbed (t_{max} of 1 hour) after oral administration with an estimated oral bioavailability of approximately 85% within the clinical dose range.

A high fat, high calorie meal delayed absorption resulting in a t_{max} of 4 h in the fed state compared to 1 h in the fasted state. Administration with food resulted in an approximately 55% decrease in C_{max} (GMR 0.45 [90% CI: 0.37,0.54]) and a 12% decrease in $AUC_{0\text{-}inf}$ (GMR 0.88 (90% CI: 0.84, 0.92)); however, this decrease is not considered clinically significant. Mavacamten may be administered with or without food.

Distribution

Specific studies to assess distribution of mavacamten have not been conducted in humans; however data are consistent with a high volume of distribution. Plasma protein binding *in vitro* of mavacamten is 93.1% and is independent of the mavacamten concentration in the range from 54.67 ng/mL to 2733 ng/mL. The blood-to-plasma concentration ratio is 0.79.

Metabolism

Mavacamten is extensively metabolised, primarily through CYP 2C19 (74%), CYP 3A4 (18%), and CYP 2C9 (7.6%). Various metabolites have been detected in human plasma. The exposure of the main metabolite MYK-1078 in human plasma was less than 4% of the exposure of mavacamten, and other minor metabolites had exposures less than 3% of the exposure of mavacamten. MYK-1078 has similar pharmacological activity compared to mavacamten. However, due to the small amounts in the plasma, this mavacamten metabolite would have minimal to no impact on the overall activity of mavacamten.

Elimination

Mavacamten is cleared from plasma primarily by metabolism through cytochrome P450 enzymes. Terminal half-life is 6-9 days in CYP 2C19 normal metabolizers (NM). Drug accumulation occurs with an accumulation ratio of about 2-fold for C_{max} and about 7-fold for AUC. At steady-state, the peak-to-trough plasma concentration ratio with once daily dosing is approximately 1.5. Intersubject pharmacokinetic (PK) variability for C_{max} and AUC shows a coefficient of variation of approximately 30 to 50%.

Following a single 25 mg dose of ^{14}C labelled mavacamten, 7% and 85% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 1% and 3% of the administered dose in the faeces and urine, respectively.

CYP 2C19 PM:

After a single dose of 15 mg mavacamten, C_{max} and AUC_{inf} increased by 1.47-fold and 3.41-fold, respectively, in CYP 2C19 poor metabolizers (PM) compared to NM. Mean half-life is prolonged in CYP 2C19 PM compared to NM (23 days *versus* 6-9 days, respectively). The incidence of CYP 2C19 PM ranges from approximately 2% in Caucasian to 18% in Asian populations.

Linearity/non-linearity

Exposure to mavacamten increased approximately dose-proportionally between 2 mg and 48 mg.

Kinetics in specific patient groups

In a population pharmacokinetic analysis, no clinically relevant differences in the PK of mavacamten were found concerning age, sex, race or ethnicity.

Hepatic impairment

A single dose PK study was conducted in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, as well as a control group with normal hepatic function. Mavacamten exposures (AUC) increased 3.2-fold and 1.9-fold in patients with mild and moderate impairment, respectively, compared to patients with normal hepatic function. There was no effect of hepatic function on C_{max}, consistent with no change in the rate of absorption and/or volume of distribution. A dedicated PK study has not been conducted in patients with severe (Child-Pugh class C) hepatic impairment.

Renal impairment

Approximately 3% of a mavacamten dose is excreted in the urine as parent drug. A population PK analysis, which comprised eGFR down to 29.5 mL/min/1.73m^2, demonstrated no clinically relevant influence of the renal function on the mavacamten exposure. No data are available in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2).

Preclinical data

Safety pharmacology

Preclinical studies to investigate the observed QTc prolongation in healthy hearts in animals demonstrated no proarrhythmic and/or torsadogenic potential either *in vivo*, *in vitro*, and/or *in silico*, and confirmed that the QTc prolongation observed in healthy hearts is not the result of an off-target direct effect of mavacamten on late-repolarization currents like hERG ion channel activity and/or trafficking. The findings in healthy hearts are attributed to an adaptive response to the cardiac mechanical/functional changes (marked mechanical LV depression) occurring in response to myosin inhibition in hearts with normal physiology and LV contractility.

Single and repeat-dose toxicity

The nonclinical safety profile of mavacamten has been evaluated in rats and dogs dosed for up to 6 and 9 months, respectively. Noted toxicities, including echocardiographic findings of reduced systolic performance and cardiac dilation, death due to heart failure, and, in rats, increased heart weights likely secondary to cardiac hypertrophy in response to decreased contractility, were consistent with the mavacamten mechanism of action and primary pharmacological activity. Other findings included cardiac osseous metaplasia in rats and QTc prolongation in dogs. Plasma exposures (AUC) at the no-observed-adverse-effect level (NOAEL) in rats and dogs, respectively, are lower than those in humans at the maximum recommended human dose (MRHD).

Genotoxicity

Mavacamten was not found to be genotoxic in a reverse mutation bacterial test (Ames test), a human *in vitro* lymphocyte clastogenicity assay, or a rat *in vivo* micronucleus assay. The C_{max} exposure at the highest dose tested in the *in vivo* study was 1x relative to the MRHD.

Carcinogenicity

There was no evidence of carcinogenicity at the highest mavacamten doses tested in a 6-month rasH2 transgenic mouse study or a 2-year rat study. Exposures (AUC) in mice were up to 3-fold

higher compared to the MHRD, while exposures (AUC) in rats were up to 0.2-fold higher compared to the MRHD.

Reproductive toxicity

Fertility

In reproductive toxicity studies, there was no evidence of effects of mavacamten on mating and fertility in male or female rats or in the viability and fertility of offspring of dams at any dose tested. Plasma exposures (AUC) of mavacamten at the highest doses tested were less than in humans at the MRHD.

Embryo-foetal development

When mavacamten was administered orally to pregnant rats during the period of organogenesis, decreased mean foetal body weight and increases in post-implantation loss and foetal malformations (visceral and skeletal) were observed in the highest dose group. Visceral malformations (heart malformation in foetuses, including one total situs inversus) and an increased incidence of skeletal malformations (mainly fused sternebrae) were observed.

When mavacamten was administered orally to pregnant rabbits during the period of organogenesis, foetal malformations (visceral and skeletal) were increased at doses of 1.2 mg/kg/day and higher. Visceral findings consisted of malformations of the great vessels (dilatation of pulmonary trunk and/or aortic arch) noted in 4 foetuses from 4 litters at 2.0 mg/kg/day. Skeletal malformations consisted of higher incidences of fused sternebrae (38 foetuses from 10 litters) at 2.0 mg/kg/day.
Plasma exposure (AUC) at the no-effect dose for embryo-foetal development in rats and rabbits is less than that in humans at the MRHD.

Pre- and post-natal development

In a pre- and post-natal development study, mavacamten was administered to pregnant rats from gestation Day 6 to lactation/post-partum Day 20. No adverse effects were observed in the dams or offspring exposed daily from before birth (in utero) through lactation. The maternal exposure was inferred from the embryo-foetal developmental toxicity study dosed at the same level, and the exposure was less than the MRHD.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

Instructions for handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68477 (Swissmedic)

Packs

Camzyos 2.5 mg: 28 hard capsules (B)
Camzyos 5 mg: 28 hard capsules (B)
Camzyos 10 mg: 28 hard capsules (B)
Camzyos 15 mg: 28 hard capsules (B)

Marketing authorisation holder

Bristol-Myers Squibb SA, Steinhausen

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